



(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
04.05.2005 Bulletin 2005/18

(51) Int Cl.7: **A61K 31/5575, A61P 17/00,**
A61P 17/04, A61P 27/02
// C07C405:00

(21) Application number: **03784565.8**

(22) Date of filing: **07.08.2003**

(86) International application number:
PCT/JP2003/010051

(87) International publication number:
WO 2004/014394 (19.02.2004 Gazette 2004/08)

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IT LI LU MC NL PT RO SE SI SK TR
Designated Extension States:
AL LT LV MK

(30) Priority: **09.08.2002 JP 2002234011**

(71) Applicants:
• **TAISHO PHARMACEUTICAL CO., LTD**
Tokyo 170-8633 (JP)
• **Sato, Fumie**
Fujisawa-shi, Kanagawa 251-0026 (JP)

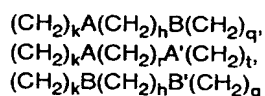
(72) Inventors:
• **SATO, Fumie**
Fujisawa-shi, Kanagawa 251-0026 (JP)

• **ARAI, Iwao,**
c/o TAISHO PHARMACEUTICAL CO., LTD.
Toshima-ku, Tokyo 170-8633 (JP)
• **TAKANO, Norikazu,**
c/o TAISHO PHARMACEUTICAL CO.Ltd
Toshima-ku, Tokyo 170-8633 (JP)
• **TANAMI, Tohru,**
c/o TAISHO PHARMACEUTICAL CO., LTD.
Toshima-ku, Tokyo 170-8633 (JP)
• **YAGI, Makoto,**
c/o TAISHO PHARMACEUTICAL CO., LTD.
Toshima-ku, Tokyo 170-8633 (JP)

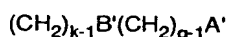
(74) Representative: **HOFFMANN EITLE**
Patent- und Rechtsanwälte
Arabellastrasse 4
81925 München (DE)

(54) **ANTIPRURITIC AGENT**

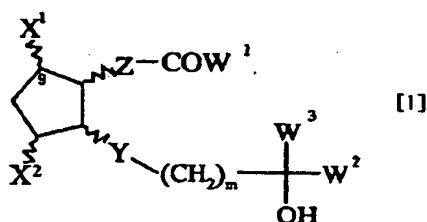
(57) A pharmaceutical preparation for preventing or treating pruritic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1]



or



wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;



wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula

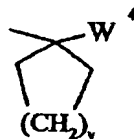
A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula S(O)_u wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅

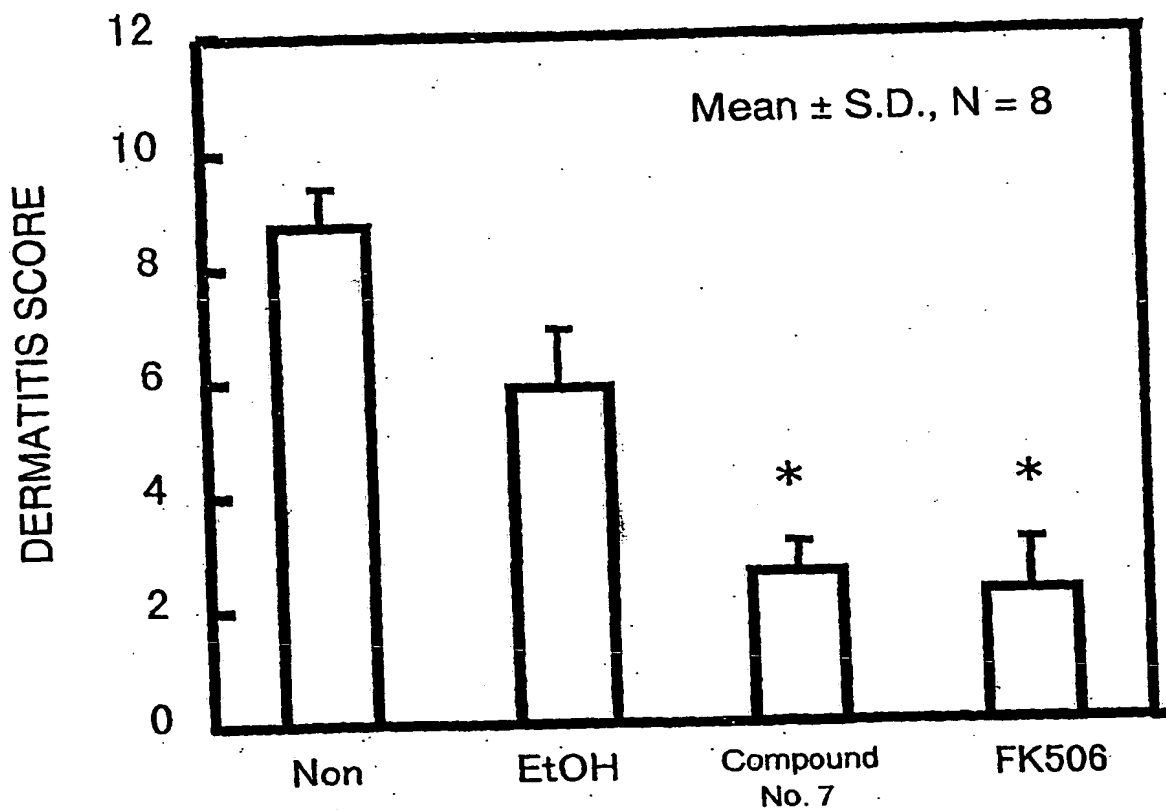
alkyl group substituted by C₃₋₁₀ cycloalkyl group(s),
or a group represented by the formula



wherein W^4 is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

W^3 is a hydrogen atom or a methyl group, or W^3 when taken together with W^2 and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

FIG. 1



Description

TECHNICAL FIELD

[0001] This invention relates to pharmaceutical preparations for preventing or treating pruritic symptoms (the pharmaceutical preparations are hereunder sometimes referred to as antipruritics), more particularly to antipruritics effective in eliminating the itch sensation due to atopic symptoms.

BACKGROUND ART

[0002] Recent years have seen a rapid increase in the number of patients with pruritic symptoms as from atopic dermatitis, atopic conjunctivitis and senile xerosis. These diseases are accompanied by an intense itch sensation of obscure etiology and itch-evoked scratching behavior is believed to induce inflammations in mucous membranes or skin. Therefore, eliminating an itch sensation is crucial to the elimination of those symptoms.

[0003] Pharmaceutical preparations conventionally used to treat chronic dermatitis include steroids for external application, antihistamines and antiallergics. However, the use of steroids is restricted for the side effects they may cause as a result of prolonged continued use, and no antihistamines or antiallergics have been obtained that are completely satisfactory in terms of therapeutic efficacy.

[0004] Heretofore, antipruritics have been assessed by administering histamine, serotonin and other pruritogens into the skin of animals and measuring their itch-evoked scratching behavior. However, it was recently reported that the manifestation of an itch due to pruritic symptoms as in atopic dermatitis is not simply the reaction caused by histamine, etc. that are released from mast cells (J. Dermatological Science 25, 20-28, 2001).

[0005] Therefore, it is desired to develop antipruritics that depend on a new mechanism of action for preventing and treating pruritic symptoms as in atopic dermatitis.

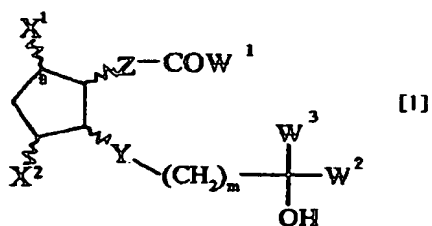
[0006] A prostaglandin has been reported to be a prurigenic component (J. Am. Acad. Dermatol. 47, 28-32, 2002) but its use as an antipruritic is not known.

DISCLOSURE OF THE INVENTION

[0007] An object, therefore, of the present invention is to provide pharmaceutical preparations that depend on a new mechanism of action for preventing or treating pruritic symptoms, in particular, atopic symptoms.

[0008] With a view to attaining this object, the present inventors made an investigation adopting the method of assessment to be described later and found that certain kinds of prostaglandins had an outstanding antipruritic effect and were particularly effective in controlling the itch sensation accompanying atopic symptoms. The present invention has been accomplished on the basis of this finding.

[0009] Thus, according to one embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating pruritic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1]



wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

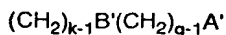
Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula

(CH₂)ₖA(CH₂)ₕB(CH₂)ₑ,

(CH₂)ₖA(CH₂)ᵣA'(CH₂)ₜ,

(CH₂)ₖB(CH₂)ₕB'(CH₂)ₑ

or

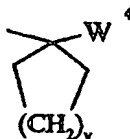


wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group; B and B' which may be the same or different represent an oxygen atom or a group represented by the formula S (O)_u wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

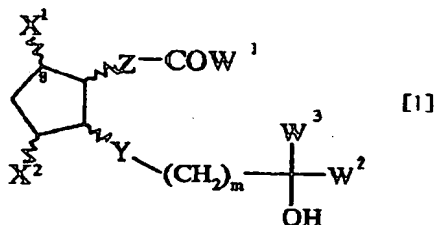
W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by a C₃₋₁₀ cycloalkyl group, or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

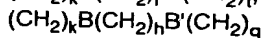
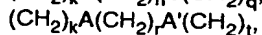
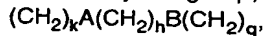
W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0010] According to another embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1]

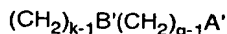


wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula



or



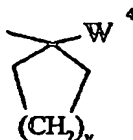
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula S (O)_u wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

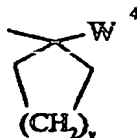
W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0011] According to yet another embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating pruritic or atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1], provided that 7-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-(5Z)-5-heptenic acid is excluded, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0012] According to still another embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating pruritic or atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein X¹ is a halogen atom, X² is a hydroxyl group and Y is an ethynylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0013] According to a still further embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating pruritic or atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein X¹ is a halogen atom, X² is a hydroxyl group and Y is a vinylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0014] According to yet another embodiment of the invention, there is provided a pharmaceutical preparation for preventing or treating pruritic or atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4; W³ is a hydrogen atom or a methyl group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

[0015] According to a further embodiment of the invention, there is provided such a pharmaceutical preparation for preventing or treating atopic symptoms wherein the atopic symptoms are those in atopic dermatitis or atopic conjunctivitis.

[0016] According to a still further embodiment of the invention, there is provided such a pharmaceutical preparation for preventing or treating pruritic or atopic symptoms which is an agent for external application.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Fig. 1 shows the results with dermatitic symptoms (dermatitis scores) as observed at 4 weeks after drug

administration, in which Non refers to no treatment, EtOH ethanol, FK506 tacrolimus, and * means $p < 0.05$;

Fig. 2 shows the results of a test for suppressing spontaneous itch-evoked scratching behavior by administering compound No.3;

Fig. 3 shows the results of a test for suppressing spontaneous itch-evoked scratching behavior by administering compound No.11; and

Fig. 4 shows the results of a test for suppressing spontaneous itch-evoked scratching behavior by administering compound No.12.

BEST MODE FOR CARRYING OUT THE INVENTION

[0018] The inventors assessed the antipruritic effect of various pharmaceutical preparations on itch-evoked but spontaneous scratching behavior by measuring the itch-evoked scratching behavior of NC/Nga mice that would spontaneously develop an atopic dermatitis-like skin disease.

[0019] The numbers of scratchings done by the individual animals during 24-hr periods before and after the dermal application of pharmaceutical preparations were compared to confirm the outstanding efficacy of prostaglandins represented by formula [1].

[0020] The antipruritics of the invention are described below.

[0021] The invention is characterized as containing prostaglandin derivatives of the formula [1], pharmaceutically acceptable salts thereof or hydrates thereof as an effective ingredient.

[0022] In the formula [1], the halogen atom means a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

[0023] The vinylene group means a cis- or trans-vinylene group.

[0024] The C_{1-10} alkyloxy group represents linear or branched alkyloxy groups having 1 to 10 carbon atoms, which include, for example, a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, a butoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, a tert-pentyloxy group, a 5-methylhexyloxy group, an octyloxy group, a decyloxy group, etc.

[0025] Examples of the C_{3-10} cycloalkyloxy group include a cyclopropyloxy group, a cyclobutyloxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cycloheptyloxy group, a cyclononyloxy group, etc.

[0026] Examples of the aryloxy group include a phenoxy group, a bromophenoxy group, a chlorophenoxy group, a tolyloxy group, a cumenyloxy group, a methoxyphenoxy group, etc.

[0027] Examples of the arylalkyloxy group include a benzyloxy group, a bromobenzyloxy group, a chlorobenzyloxy group, a nitrobenzyloxy group, a dinitrobenzyloxy group, a methoxybenzyloxy group, a phenethyloxy group, a phenylpropyloxy group, a phenylpentyloxy group, etc.

[0028] The C_{1-10} alkyl group represents linear or branched alkyl groups having 1 to 10 carbon atoms, which include, for example, a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a sec-butyl group, a tert-butyl group, a pentyl group, a tert-pentyl group, an isohexyl group, a heptyl group, an octyl group, a decyl group, etc.

[0029] The C_{2-10} alkenyl group means those linear or branched alkyl groups with 2 to 10 carbon atoms which have one or more double bonds in desired positions and they may be exemplified by a vinyl group, an allyl group, a 1-propenyl group, an isopropenyl group, a 3-butenyl group, a 1,3-butadienyl group, a 7-octenyl group, etc.

[0030] The C_{2-10} alkynyl group means those linear or branched alkyl groups with 2 to 10 carbon atoms which have one or more triple bonds in desired positions and may be exemplified by an ethynyl group, a 2-propynyl group, a 2-pentynyl group, a 4-octynyl group, etc.

[0031] Examples of the C_{3-10} cycloalkyl group include unsubstituted cycloalkyl groups such as a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclononyl group, as well as those cycloalkyl groups having one or more substituents selected from among halogen atoms, C_{1-10} alkyl groups, C_{1-10} alkyloxy groups, etc. which are exemplified by a 4-fluorocyclohexyl group, a 4,4-difluorocyclohexyl group, a 4-methoxycyclohexyl group, a 2-methylcyclohexyl group, a 4-trifluoromethylcyclohexyl group, etc.

[0032] Examples of the C_{1-5} alkyl group substituted by C_{3-10} cycloalkyl group(s) include a cyclopropylmethyl group, a cyclobutylethyl group, a cyclopentylmethyl group, a cyclohexylmethyl group, a cycloheptylmethyl group, a cyclononylbutyl group, a 4-fluorocyclohexylmethyl group, etc.

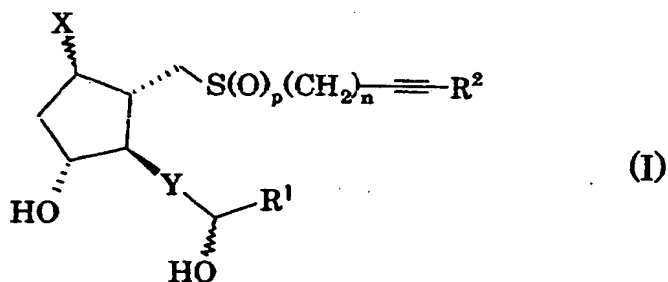
[0033] The pharmaceutically acceptable salt may be exemplified by salts with alkali metals such as sodium and potassium, salts with alkaline earth metals such as calcium and magnesium, and salts with ammonia, methylamine, dimethylamine, cyclopentylamine, benzylamine, piperidine, monoethanolamine, diethanolamine, monomethylmonoethanolamine, tromethamine, lysine, tris(hydroxymethyl)aminomethane, etc.

[0034] If Z is the formula $(CH_2)_k A (CH_2)_h B (CH_2)_q$, preferably, $k+h+q=3$, and more preferably, $k=1$, $h=1$ and $q=1$. If Z is the formula $(CH_2)_k A (CH_2)_r A' (CH_2)_t$, preferably, $k+r+t=2$, and more preferably, $k=1$, $r=1$ and $t=0$. If Z is the formula $(CH_2)_k B (CH_2)_h B' (CH_2)_q$, preferably, $k+h+q=4$, and more preferably, $k=1$, $h=2$ and $q=1$. If Z is the formula $(CH_2)_{k-1} B' (CH_2)_{q-1} A'$, preferably, $k+q=5$, and more preferably, $k=2$ and $q=3$.

[0035] Some of the prostaglandin derivatives which serve as the effective ingredient in the present invention are known compounds disclosed in the following official gazettes:

[0036] WO94/02457, WO94/08959, WO95/18101, WO99/61029, WO99/61419, WO01/19790, US5807892, JP 2-502009 A, JP 6-192218 A, JP 7-242622 A, JP 7-242623 A, JP 7-233144 A, JP 7-285929 A, JP 8-208599 A, JP 9-286775 A, JP 58-8059 A, JP 60-501813 A, JP 61-500787 A, JP 2000-95755 A, JP 2000-128858 A, JP 2000-273083 A, JP 2001-122786 A, JP 2001-89443 A, JP 2001-135944 A, and JP 2001-151749 A.

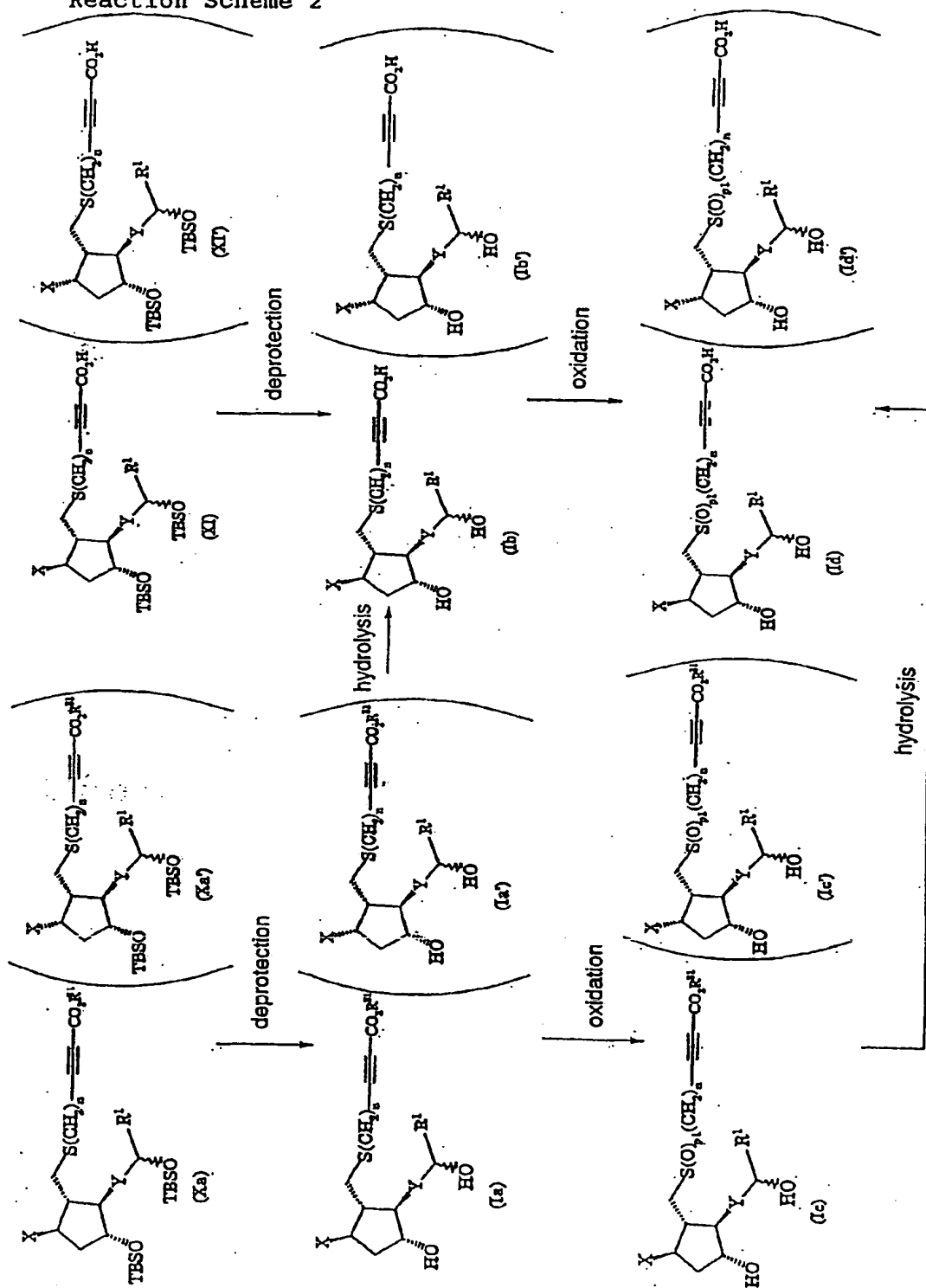
[0037] Note that prostaglandin derivatives represented by the following formula



wherein X is an α - or β -substituted halogen atom, Y is an ethylene group, a vinylene group or an ethynylene group, R¹ is a C₃₋₁₀ cycloalkyl group, a C₃₋₁₀ cycloalkyl group substituted by C₁₋₄ linear or branched alkyl group(s), or a C₄₋₁₃ cycloalkylalkyl group, R² is a group represented by CO₂R³, wherein R³ is a hydrogen atom, a C₁₋₄ linear or branched alkyl group or a C₂₋₄ linear or branched alkenyl group, n is an integer of 1 to 4, and p is 0, 1 or 2 can be produced by processes according to reaction schemes 1 and 2.



Reaction Scheme 2



(in the above reaction schemes, TBS represents a tert-butyldimethylsilyl group, Y' represents an ethylene group or a vinylene group, R³¹ represents a C₁₋₄ alkyl group or a C₂₋₄ alkenyl group, p1 represents 1 or 2, Z' represents a halogen atom, and X, Y, R¹ and n have the same meanings as defined above.)

[0038] The two reaction schemes are explained below:

(1) First, according to the method of Satoh et al. [Journal of Organic Chemistry (J. Org. Chem.), vol. 53, p. 5590 (1988)], a known compound of formula (II) is reacted with 0.8 to 2.0 equivalent amounts of a compound represented by formula (III) or (III') in an inert solvent (e.g. benzene, toluene, tetrahydrofuran, diethyl ether, methylene chloride or n-hexane) at -78 to 30°C, to give a stereospecific compound of formula (IV). In order to obtain a compound where Y is an ethylene group or a vinylene group (i.e. Y is Y'), a compound of formula (III') is employed and reaction is performed at -78 to 0°C; in order to obtain a compound where Y is an ethynylene group, a compound of formula (III) is employed and reaction is performed at 0 to 30°C.

(2) The compound of formula (IV) is reacted with 1 to 6 equivalent amounts of a compound represented by formula (V) in an organic solvent (e.g. benzene, toluene, xylene, n-hexane, n-pentane or acetone) at -78 to 100°C, optionally employing 0.05 to 2 equivalent amounts of a radical generator (e.g. azobisisobutyronitrile, azobiscyclohexanecarbonitrile, benzoyl peroxide or triethylborane), further optionally employing 1 to 5 equivalent amounts of a radical reducing agent (e.g. tributyltin hydride, triphenyltin hydride, dibutyltin hydride or diphenyltin hydride), thereby giving a compound of formula (VI). In a certain case, a compound of formula (VI) can also be obtained by performing the reaction in an organic solvent (e.g. benzene, toluene, xylene, n-hexane, n-pentane or acetone) at -78 to 100°C employing 0.05 to 2 equivalent amounts of a base (e.g. an organic amine such as triethylamine, diisopropylamine, pyridine or dimethylaniline, or a base resin such as polyvinylpyrrolidone, diisopropylaminomethyl-polystyrene or (piperidinomethyl)polystyrene).

(3) The compound of formula (VI) is reacted with 0.5 to 5 equivalent amounts of a reducing agent such as potassium borohydride, sodium borohydride, sodium cyanoborohydride, lithium tri-sec-butyl borohydride or diisobutylaluminum hydride-BHT (2,6-di-tert-butyl-p-cresol) in an organic solvent (e.g. tetrahydrofuran, diethyl ether, ethyl alcohol, methyl alcohol or toluene) at -78 to 40°C to give compounds of formulas (VII) and (VII'). These compounds of formulas (VII) and (VII') can be purified by a commonly employed separation technique such as column chromatography.

(4) The compound of formula (VII) (or formula (VII')) is mesylated or tosylated with, for example, 1 to 6 equivalent amounts of methanesulfonyl chloride or p-toluenesulfonyl chloride in a suitable solvent such as pyridine at -20 to 40°C, optionally in the presence of 0.8 to 6 equivalent amounts of 4-dimethylaminopyridine, followed by chlorination with 1 to 16 equivalent amounts of tetra-n-butylammonium chloride to give a compound of formula (VIII) (or formula (VIII')) (X is a chlorine atom). Bromination and fluorination can also be performed by ordinary methods. For example, bromination can be obtained by reacting 1 to 10 equivalent amounts of carbon tetrabromide in acetonitrile in the presence of 1 to 10 equivalent amounts each of triphenylphosphine and pyridine. Fluorination may, for example, be obtained by reacting 5 to 20 equivalent amounts of diethylaminosulfate trifluoride (DAST) in methylene chloride.

(5) The compound of formula (VIII) (or formula (VIII')) is reacted with a base (e.g. an alkyl lithium such as n-butyllithium) at a temperature between -78°C and room temperature in a suitable inert organic solvent (e.g. tetrahydrofuran or diethyl ether) and thereafter reacted with a compound of formula (IX) at -78 to 40°C to give a compound of formula (Xa) (or formula (Xa')); if the formula (IX) is replaced by carbon dioxide as the reactant, a compound of formula (XI) (or formula (XI')) can be obtained.

(6) The compound of formula (Xa) (or formula (Xa')) is freed of the hydroxyl protecting tert-butyldimethylsilyl group in methanol, ethanol, acetonitrile or a mixed solvent thereof or a mixture thereof with water under ordinary conditions employing hydrofluoric acid, pyridinium poly(hydrogenfluoride), hydrochloric acid, etc. so as to give a PG derivative of formula (Ia) (or formula (Ia')) according to the present invention.

(7) By hydrolyzing the compound of formula (Ia) (or formula (Ia')) through reaction with an enzyme in a buffer solution such as a phosphate buffer or a Tris-HCl buffer, optionally employing an organic solvent (a water-miscible one such as acetone, methanol or ethanol), a PG derivative of formula (Ib) (or formula (Ib')) claimed in the invention can be obtained. Exemplary enzymes are those produced by microorganisms (e.g. enzymes produced by microorganisms of *Candida* sp. and *Pseudomonas* sp.) and those prepared from animal organs (e.g. enzymes prepared from swine liver and pancreas). To mention specific examples of commercial enzymes, they include lipase VII (product of Sigma, derived from a microorganism of *Candida* sp.), lipase AY (product of Amano Pharmaceutical Co., Ltd., derived from a microorganism of *Candida* sp.), lipase PS (product of Amano Pharmaceutical Co., Ltd., derived from a microorganism of *Pseudomonas* sp.), lipase MF (product of Amano Pharmaceutical Co., Ltd., derived from a microorganism of *Pseudomonas* sp.), PLE (product of Sigma, prepared from swine liver), lipase II (product of Sigma, prepared from swine pancreas), and lipoprotein lipase (product of Tokyo Kasei Kogyo Co., Ltd., prepared from swine pancreas).

The amount of the enzyme to be used may be chosen as appropriate for its potency and the amount of its

substrate [formula (Ia) (or formula (Ia'))] and the usual amount is 0.1 to 20 times the weight of the substrate. The reaction temperature is 25 to 50°C, preferably 30 to 40°C.

A PG derivative of formula (Ib) (or formula (Ib')) claimed in the invention may be obtained by hydrolyzing the compound of formula (Ia) (or formula (Ia')) with a base in a solvent commonly employed in hydrolysis. Exemplary bases that can be employed are lithium hydroxide and potassium carbonate, and exemplary solvents include acetonitrile, acetone, methanol, ethanol, water and mixtures thereof.

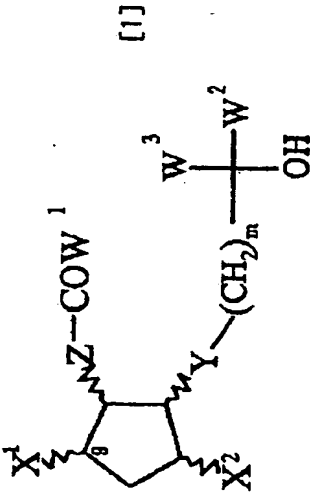
A PG derivative of formula (Ib) (or formula (Ib')) claimed in the invention can also be obtained by deprotecting the compound of formula (XI) (or formula (XI')) as in (6) above.

(8) The compound of formula (Ia) (or formula (Ia')) is reacted with an oxidizing agent such as sodium metaperiodate, hydrogen peroxide, peracetic acid, m-chloroperbenzoic acid and tert-butyl hydroperoxide in diethyl ether, methanol, ethanol, methylene chloride, water or mixtures thereof at -20 to 50°C to give a PG derivative of formula (Ic) (or formula (Ic')) claimed in the invention.

(9) By hydrolyzing the compound of formula (Ic) (or formula (Ic')) as in (7) above, a PG derivative of formula (Id) (or formula (Id')) claimed in the invention is obtained. A PG derivative of formula (Id) (or formula (Id')) claimed in the invention can also be obtained by oxidizing the formula (Ib) (or formula (Ib')) as in (8) above.

[0039] The following compounds can be listed as representative compounds of the formula [1] claimed in the invention.

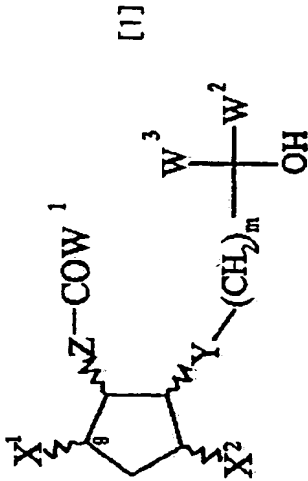
Table 1



Compound No.	X1	X2	Y	A	B	m	k	h	q	u	W1	W2	W3	8-position	9-position	11-position	12-position	OH
1	Cl	HO	CH2CH2	Z-CH=CH	S	0	1	1	1	0	OMe	cyc6	H	α	β	α	β	α
2	Cl	HO	CH2CH2	Z-CH=CH	S	0	1	1	1	0	OH	cyc6	H	α	β	α	β	α
3	Cl	HO	E-CH=CH	Z-CH=CH	O	0	1	1	1	1	OH	cyc6	H	α	β	α	β	α
4	Cl	HO	C≡C	Z-CH=CH	O	0	1	1	1	1	OtBu	cyc6	H	α	β	α	β	α
5	Cl	HO	C≡C	CH2CH2	O	0	1	1	1	1	OtBu	cyc6	H	α	β	α	β	α
6	Cl	HO	C≡C	CH2CH2	S	0	1	1	1	0	OMe	cyc6	H	α	β	α	β	α
7	Cl	HO	C≡C	CH2CH2	S	0	1	1	1	0	OH	cyc6	H	α	β	α	β	α
8	Cl	HO	C≡C	Z-CH=CH	O	0	1	1	1	1	OH	cyc6	H	α	β	α	β	α
9	H	HO	C≡C	CH2CH2	S	0	1	1	1	0	OH	cyc6	H	α	β	α	β	α
10	Cl	HO	C≡C	C≡C	O	0	1	1	1	1	OH	cyc6	H	α	β	α	β	α
11	Cl	HO	CH2CH2	Z-CH=CH	O	0	1	1	1	1	OH	cyc6	H	α	β	α	β	α
12	Cl	HO	E-CH=CH	CH2CH2	S	0	1	1	1	0	OH	cyc6	H	α	β	α	β	α

E-CH=CH: trans-vinylene group
Z-CH=CH: cis-vinylene group
cyc6: cyclohexyl group

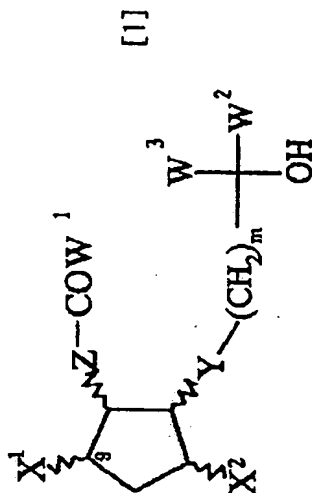
Table 2



Compound No.	X1	X2	Y	A	A'	m	k	r	t	W1	W2	W3	8-positio	9-positio	11-positio	12-positio	OH
13	Cl	HO	E-CH=CH	CH2CH2	C≡C	0	1	1	0	OMe	cyc5m	H	α	α	α	β	α
14	Cl	HO	C≡C	CH2CH2	C≡C	0	1	2	0	OH	cyc6	H	α	β	α	β	α
15	Cl	HO	C≡C	CH2CH2	C≡C	0	1	1	0	OH	cyc6	H	α	β	α	β	α
16	Cl	HO	C≡C	CH2CH2	E-CH=CH	0	1	1	0	OMe	cyc6	H	α	β	α	β	α
17	Cl	HO	C≡C	CH2CH2	E-CH=CH	0	1	1	0	OPr	cyc6	H	α	β	α	β	α
18	Cl	HO	C≡C	CH2CH2	E-CH=CH	0	1	1	0	OBu	cyc6	H	α	β	α	β	α
19	Cl	HO	C≡C	CH2CH2	C≡C	0	1	1	0	OBu	cyc6	H	α	β	α	β	α
20	Cl	HO	C≡C	CH2CH2	C≡C	0	1	1	1	OMe	Me-cyc6	H	α	β	α	β	α

Z-CH=CH: cis-vinylene group
E-CH=CH: trans-vinylene group
cyc6: cyclohexyl group
Me-cyc6: 2-methylcyclohexyl group
cyc5m: cyclopentylmethyl group

Table 3



Compound No.	X1	X2	Y	B	B'	m	k	h	q	u	W1	W2	W3	8- positio	9- positio	11- positio	12- positio	OH
21	Cl	HO	C≡C	S	O	0	1	2	1	0	OMe	cyc6	H	α	β	α	β	α
22	Cl	HO	C≡C	S	O	0	1	2	1	0	OH	cyc6	H	α	β	α	β	α
23	Cl	HO	C≡C	S	S	0	1	2	1	0	OMe	cyc6	H	α	β	α	β	α
24	Cl	HO	C≡C	S	S	0	1	2	1	0	OMe	cyc6	H	α	α	α	β	α
25	Cl	HO	C≡C	S	S	0	1	2	1	0	OH	cyc6	H	α	β	α	β	α
26	Cl	HO	C≡C	S	O	0	1	2	1	0	OMe	diF-cyc6	H	α	β	α	β	α
27	Cl	HO	C≡C	S	O	0	1	2	1	0	OH	diF-cyc6	H	α	β	α	β	α
28	Cl	HO	C≡C	S	O	0	1	2	1	0	OMe	CF3-cyc6	H	α	β	α	β	α
29	Cl	HO	C≡C	S	O	0	1	2	1	0	OH	CF3-cyc6	H	α	β	α	β	α
30	Cl	HO	C≡C	S	S	0	1	3	1	0	OMe	cyc6	H	α	β	α	β	α

cyc6 : cyclohexyl group
 diF-cyc6 : difluorocyclohexyl group
 CF3-cyc6 : 4-trifluoromethylcyclohexyl group

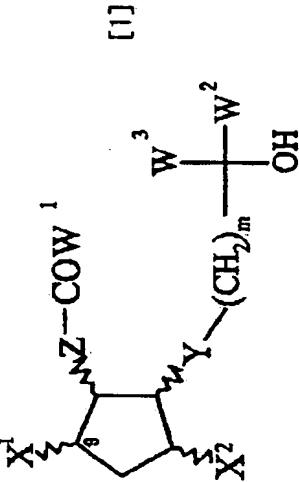


Table 4

Compound No.	X1	X2	Y	A'	B'	m	k	q	u	W1	W2	W3	8-position	9-position	11-position	12-position	OH
31	Cl	HO	C≡C	CH2CH2	S	0	2	3	0	OMe	cyc6	H	α	β	α	β	α
32	Cl	HO	C≡C	CH2CH2	S	0	2	3	0	OH	cyc6	H	α	β	α	β	α
33	Cl	HO	E-CH=CH	CH2CH2	S	0	1	4	0	OMe	cyc6	H	α	β	α	β	α
34	Cl	HO	E-CH=CH	CH2CH2	S	0	4	1	0	OMe	cyc6	H	α	β	α	β	α
35	Cl	HO	E-CH=CH	CH2CH2	S	0	3	2	0	OMe	cyc6	H	α	β	α	β	α
36	Cl	HO	E-CH=CH	CH2CH2	S	0	2	3	0	OH	cyc6	H	α	β	α	β	α
37	Cl	HO	CH2CH2	CH2CH2	S	0	2	3	0	OMe	cyc6	H	α	β	α	β	α
38	Cl	HO	CH2CH2	CH2CH2	S	0	2	3	0	OH	cyc6	H	α	β	α	β	α
39	Cl	HO	C≡C	C≡C	S	0	2	3	0	OH	cyc6	H	α	β	α	β	α
40	Cl	HO	C≡C	CH2CH2	S	0	2	1	0	OH	cyc6	H	α	β	α	β	α

E-CH=CH: trans-vinylene group
cyc6 : cyclohexyl group

[0040] As long as they can relieve or eliminate an itch sensation, the antipruritics of the invention are not limited in any way but they are particularly effective against the atopy-evoked itching. From this viewpoint, the antipruritics of the invention encompass pharmaceutical preparations for preventing or treating atopic symptoms.

[0041] In the invention, the term "pruritic symptoms" means those symptoms which involve circumscribed or generalized itching and associated inflammations on the skin and mucous membranes. Examples include scabies, urticaria, eczema, xerosis (senile xeroderma and asteatotic eczema), psoriasis, dermal pruritus, and prurigo.

[0042] In the invention, the term "atopic symptoms" means those symptoms which involve atopy-evoked, circumscribed or generalized itching and associated inflammations on the skin and mucous membranes; in other words, the term refers to atopy-evoked pruritic symptoms (including nervous pruritus). Examples include atopic dermatitis and atopic conjunctivitis.

[0043] In the invention, the term "atopic dermatitis" refers to a disorder that involves itching eczema as a principal lesion which undergoes repeated exacerbation and remission; this is highly likely to develop in individuals predisposed to atopy.

[0044] The antipruritics of the invention can be administered either orally, parenterally or topically.

[0045] The dose to be administered of the effective ingredient in the antipruritics of the invention can be adjusted as appropriate for the body weight of the patient, his or her age, sex, etc. Usually, the dosage is 1 ng to 10 mg, preferably 0.1 to 100 µg, per administration and one to several administrations are tolerated per day.

[0046] The antipruritics of the invention can be prepared as pharmaceutical compositions employing the effective ingredient in combination with carriers, vehicles and other additives that are employed in ordinary pharmaceutical formulation procedures.

[0047] Exemplary carriers and vehicles for pharmaceutical formulation procedures include water, ethanol, lactose, microcrystalline cellulose, liquid paraffin, hydrogenated oils, beeswax, squalane, stearyl alcohol, ethylene glycol and others that are in common use.

[0048] Exemplary additives are commonly employed ingredients including disintegrants (e.g. starch), binders (hydroxypropyl cellulose and low-substituted hydroxypropyl cellulose), lubricants (e.g. talc and glycerol-stearate), antioxidants, preservatives (e.g. parabens), coating agents (e.g. gelatin and hydroxypropyl cellulose), coloring agents, flavoring/odorizing agents, skin color lightening agents (e.g. sodium ellagate), surfactants (e.g. sorbitan fatty acid esters), plasticizers, humectants (e.g. glycerin, propylene glycol, polyethylene glycol and hyaluronic acid), etc.

[0049] The antipruritics of the invention can be administered in various dosage forms such as those for internal application, injections and those for external application (nasal drops and eye drops), as specifically exemplified by tablets, granules, powders, capsules, liquids, gels, plasters, ointments, creams, cataplasms and aerosols.

[0050] Dosage forms for external application are preferred for the various advantages they have, such as direct applicability to the diseased area, ease of application and a reduced possibility for the occurrence of systemic side effects.

[0051] Dosage forms "for external application" include liquids for external application, aerosols, powders for external application, ointments, creams, gels, plasters, cataplasms, etc.

[0052] The following examples and test examples are provided for the purpose of further illustrating the present invention but are in no way to be taken as limiting. Various alterations and modifications can be made by the skilled artisan on the basis of the foregoing description of the invention and are also encompassed by the invention.

[0053] Unless otherwise noted, the drug concentration (%) means w/v% (weight/volume%).

Example 1:

[0054] The ingredients listed below were weighed and mixed uniformly; then, purified water and ethanol were added in the volumes indicated below to make 1000 ml of a liquid.

Compound No.7	0.1 g
Ethanol	200 ml
Purified water	800 ml

Example 2:

[0055] The ingredients listed below were weighed and emulsified uniformly; then, a flavoring agent was added to make 500 g of a cream.

Compound No.3	0.5 g
---------------	-------

(continued)

Carbinoxamine maleate	5 g
Sodium ellagate	5 g
Sodium hyaluronate	3 g
Methyl paraben	2 g
Purified water	218.5 g
Liquid paraffin(#70)	50 g
Squalane	100 g
Cetostearyl alcohol	60 g
Beeswax	20 g
Glycerol monostearate	15 g
Sorbitan monolaurate	20 g
Propyl paraben	1 g

Test Example 1 : Effect on the spontaneous, itch-evoked scratching behavior of NC mice

(Method)

[0056] About 20-week old NC/Nga mice each weighing about 30 g and manifesting atopic dermatitis were purchased from SLC and subjected to the following experiment. A magnet was buried in both hind paws of each mouse and by detecting its magnetism, the movement of the paws was measured with an itch measuring system (product of Neuroscience; when the mouse makes an action, the magnets move accordingly and a current flows through the coil; the moving magnets cause a change in the current, which is detected, measured and analyzed). Among the scratching actions, those lasting 1.5 seconds or longer were considered itch-evoked and their number was counted continuously. Since the itch-evoked scratching behavior had a diurnal rhythm, the diurnal rhythm of each individual animal was measured for 24 hours of the day before test and only after that, each of the test drugs dissolved in 100% ethanol was applied to the dorsal skin in a dose of 0.2 ml/mouse. The subsequent 24-hr itch-evoked scratching behavior was measured and the number of itch-evoked scratchings after drug administration was compared with the initial count. The experimental data was processed to calculate the percent itch suppression on the basis of the total 24-hr itch-evoked scratching counts before and after drug application. For significance testing, the itch-evoked scratching counts that were obtained before and after drug application from individual animals in each group treated with a specific concentration of drug were processed by a paired t-test.

$$\text{Percent itch suppression (\%)} = \frac{(\text{itch-evoked scratching count before drug application} - \text{itch-evoked scratching count after drug application}) \times 100}{\text{itch-evoked scratching count before drug application}}$$

(Results)

[0057] The structures of the compounds used in the test are shown below and the test results are shown in Table 5.

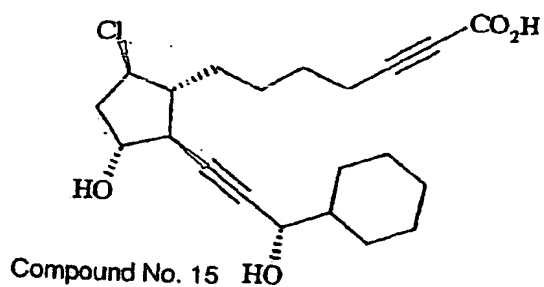
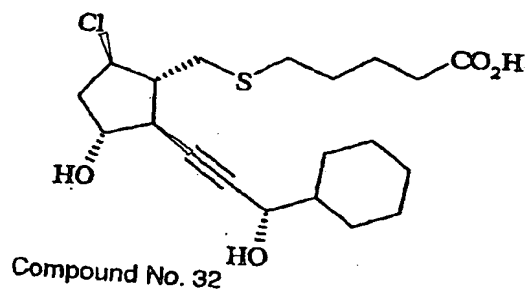
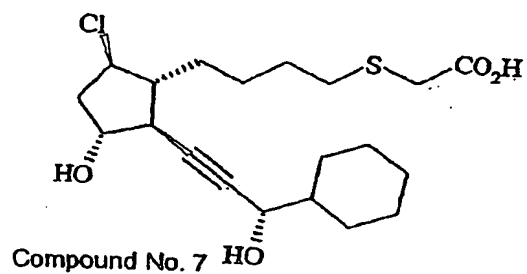
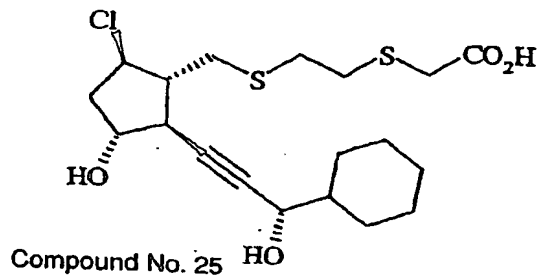
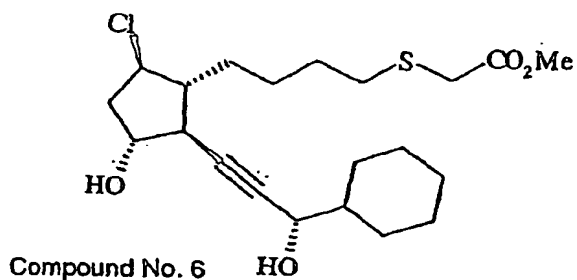


Table 5

Compound	Concentration (%)	Inhibition rate (%)	Efficacy
EtOH	100	10.2	NS
6	0.0001	32.26	*
7	0.000001	43.26	**
15	0.000001	34.61	*
25	0.00001	21.51	*
32	0.00001	41.76	**
* : P<0.05, ** : P<0.01			

Test Example 2: Effect on dermatitis manifesting NC mouse models

[0058] By suitably modifying a method known to the skilled artisan (Jpn. J. Pharmacol. 76, 175-183 (1998) Jun Hiroi, et al. Effects of Tacrolimus Hydrate (FK-506) Ointment on Spontaneous Dermatitis in NC/Nga Mice), the following test was conducted in order to confirm the antipruritic effect of compounds of the invention.

(Method)

[0059] Animals: Four-week old SPF NC mice (male) were purchased from Japan SLC; right after their arrival, the SPF NC mice were kept together with dermatitis manifesting male NC mice (older than 20 weeks) for 2 weeks under the following conditions so as to induce itch-evoked scratching behavior. A group of mice manifesting dermatitis and another group of mice not manifesting dermatitis, each consisting of four animals, were allowed to cohabit in a sawdust cage (34 x 17 x 39 cm) and kept in an animal house set at room temperature ($23 \pm 3^\circ\text{C}$) and at a humidity of $55 \pm 15\%$ under illumination for 12 hours (from 7:00 am to 7:00 pm).

[0060] After 2-wk cohabitation, the purchased mice were taken out of the cage and transferred into another cage, where a group of 8 animals were kept for about 14 weeks. Immediately before the application of a drug, the mice were reshuffled so that the dermatitis scores would be equal among all cages and then kept, four animals per cage.

[0061] Tacrolimus was purchased from Fujisawa Pharmaceutical Co., Ltd. for use in the experiment.

Drug administration: To the dorsal backs of the 20-wk NC mice that were induced to manifest dermatitis as the result of cohabitation with the spontaneous dermatitis manifesting NC mice, 100% ethanol, compound No. 7 (0.01%) dissolved in 100% ethanol or tacrolimus (0.1%) dissolved in 100% ethanol was applied from an Eppendorf pipette in 200- μl doses seven times a week for a period of 4 weeks. The non-treatment group was not given any treatment. Each test group consisted of 8 animals that were observed for any dermatitic symptoms.

Dermatitis score: Dermatitis symptoms were observed and measured once a week.

[0062] Four factors, smoothness of fur, loss of hair, bleeding and scab formation, were rated by the following scores: 0, no symptom; 1, mild symptom; 2, moderate symptom; 3, severe symptom (minimum sum, 0; maximum sum, 12).

(Results)

[0063] The results of observation of dermatitic symptoms are shown in Fig. 1.

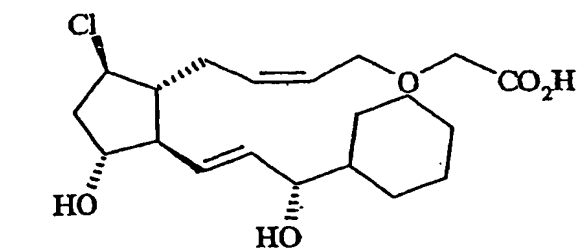
[0064] The groups administered with tacrolimus and compound No. 7 showed significant dermatitis score suppressing action compared to the vehicle group.

Test Example 3: Effect on the spontaneous, itch-evoked scratching behavior of NC mice

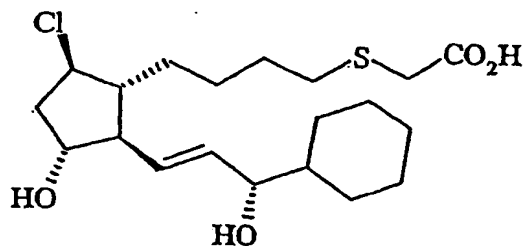
(Experimental)

[0065] About 20-week old NC/Nga mice each weighing about 30 g and manifesting atopic dermatitis were purchased from SLC and subjected to the following experiment. A magnet was buried in both hind paws of each mouse and by detecting its magnetism, the movement of the paws was measured with an itch measuring system (product of Neuroscience). Among the scratching actions, those lasting 1.5 seconds or longer were considered itch-evoked and their number was counted continuously. Since the itch-evoked scratching behavior had a diurnal rhythm, the diurnal rhythm of each individual animal was measured for 24 hours of the day before test and only after that, compound No. 3 (0.1%), compound No. 11 (0.1%) or compound No. 12 (0.1%) dissolved in 100% ethanol was applied to the dorsal skin in a dose of 0.2 ml/mouse. The subsequent 24-hr itch-evoked scratching behavior was measured and the number of itch-evoked scratchings after drug administration was compared with the initial count. The structures of the test compounds are shown below and the changes with time in the spontaneous itch-evoked scratching counts, as well as the 24-hr total spontaneous itch-evoked scratching counts before and after administration of a compound are shown in Figs. 2-4.

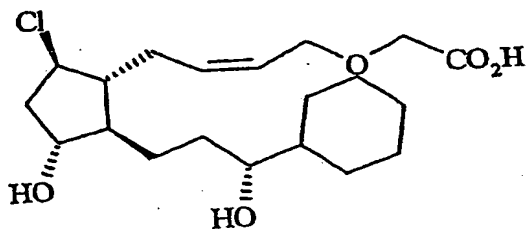
[0066] For significance testing, the itch-evoked scratching counts that were obtained before and after drug application from individual animals in each group treated with a specific concentration of drug were processed by a paired t-test.



Compound No. 3



Compound No. 12



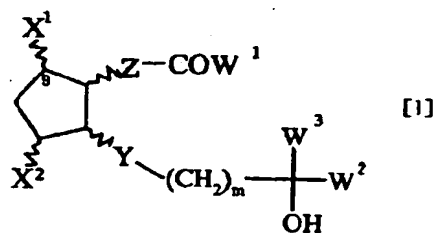
Compound No. 11

INDUSTRIAL APPLICABILITY

[0067] Having enabled reducing the frequency of itch-evoked scratching behavior that induces dermatitis, this invention successfully provides pharmaceutical preparations that can prevent or ameliorate various cases of dermatitis including atopic dermatitis, atopic conjunctivitis, scabies, urticaria and xerosis.

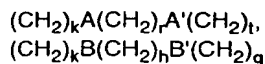
Claims

1. A pharmaceutical preparation for preventing or treating pruritic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1]

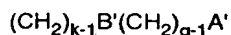


wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula (CH₂)_kA(CH₂)_hB(CH₂)_q.



or



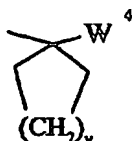
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $\text{S}(\text{O})_u$ wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

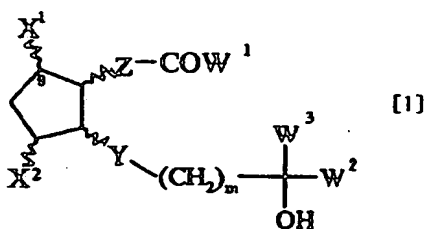
W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

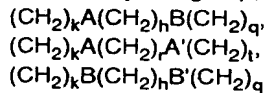
W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

2. A pharmaceutical preparation for preventing or treating atopic symptoms which contains as an effective ingredient a prostaglandin derivative represented by formula [1]

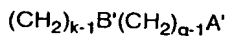


wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula



or



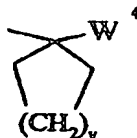
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $\text{S}(\text{O})_u$ wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkoxy group, a C₃₋₁₀ cycloalkoxy group, an aryloxy group or an arylalkoxy group;

W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

3. The pharmaceutical preparation according to claim 1 or 2 which contains as an effective ingredient a prostaglandin derivative represented by formula [1], provided that 7-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-(5Z)-5-heptenic acid is excluded, a pharmaceutically acceptable salt thereof or a hydrate thereof.

4. The pharmaceutical preparation according to claim 1 or 2 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(\text{CH}_2)_k\text{A}(\text{CH}_2)_h\text{B}(\text{CH}_2)_q$ wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer of 1 to 4, A is an ethylene group, a vinylene group or an ethynylene group, B is an oxygen atom or a group represented by formula $\text{S}(\text{O})_u$ wherein u is an integer of 0 to 2, a pharmaceutically acceptable salt thereof or a hydrate thereof.

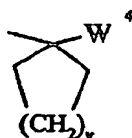
5. The pharmaceutical preparation according to claim 4 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(\text{CH}_2)_k\text{A}(\text{CH}_2)_h\text{B}(\text{CH}_2)_q$ wherein k, h and q are such that $k + h + q = 3$, a pharmaceutically acceptable salt thereof or a hydrate thereof.

6. The pharmaceutical preparation according to any one of claims 1 to 3 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(\text{CH}_2)_k\text{A}(\text{CH}_2)_r\text{A}'(\text{CH}_2)_t$ wherein k is an integer of 1 to 4, r is an integer of 0 to 4, t is an integer of 1 to 4, A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

7. The pharmaceutical preparation according to claim 6 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(\text{CH}_2)_k\text{A}(\text{CH}_2)_r\text{A}'(\text{CH}_2)_t$ wherein k, r and t are such that $k + r + t = 2$, a pharmaceutically acceptable salt thereof or a hydrate thereof.

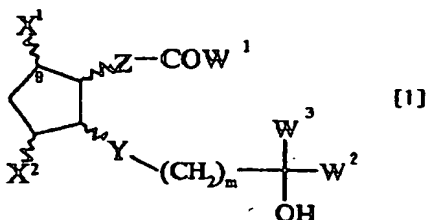
8. The pharmaceutical preparation according to claim 1 or 2 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(\text{CH}_2)_k\text{B}(\text{CH}_2)_h\text{B}'(\text{CH}_2)_q$ wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer of 1 to 4, B and B' which may be the same or different represent an oxygen atom or a group represented by formula $\text{S}(\text{O})_u$ wherein u is an integer of 0 to 2, a pharmaceutically acceptable salt thereof or a hydrate thereof.

9. The pharmaceutical preparation according to claim 8 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(CH_2)_k B'(CH_2)_h B'(CH_2)_q$ wherein k, h and q are such that $k + h + q = 4$, a pharmaceutically acceptable salt thereof or a hydrate thereof.
10. The pharmaceutical preparation according to claim 1 or 2 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(CH_2)_{k-1} B'(CH_2)_{q-1} A'$ wherein k is an integer of 1 to 4, q is an integer of 1 to 4, A' is an ethylene group, a vinylene group or an ethynylene group, B' is an oxygen atom or a group represented by formula $S(O)_u$ wherein u is an integer of 0 to 2, a pharmaceutically acceptable salt thereof or a hydrate thereof.
11. The pharmaceutical preparation according to claim 10 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] in which Z is $(CH_2)_{k-1} B'(CH_2)_{q-1} A'$ wherein k and q are such that $k + q = 5$, a pharmaceutically acceptable salt thereof or a hydrate thereof.
12. The pharmaceutical preparation according to any one of claims 1 to 11 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein X¹ is a halogen atom, X² is a hydroxyl group and Y is an ethynylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.
13. The pharmaceutical preparation according to any one of claims 1 to 11 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein X¹ is a halogen atom, X² is a hydroxyl group and Y is a vinylene group, a pharmaceutically acceptable salt thereof or a hydrate thereof.
14. The pharmaceutical preparation according to any one of claims 1 to 13 which contains as an effective ingredient a prostaglandin derivative represented by formula [1] wherein W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



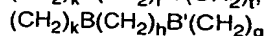
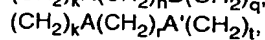
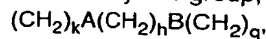
wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4; W³ is a hydrogen atom or a methyl group, a pharmaceutically acceptable salt thereof or a hydrate thereof.

15. The pharmaceutical preparation according to any one of claims 2 to 14 wherein the atopic symptoms are those in atopic dermatitis or atopic conjunctivitis.
16. The pharmaceutical preparation according to any one of claims 1 to 15 which is an agent for external application.
17. A method of preventing or treating pruritic symptoms which comprises administering to a mammal a prophylactically or therapeutically effective amount of a prostaglandin derivative represented by formula [1]

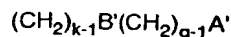


wherein X^1 and X^2 which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula



or



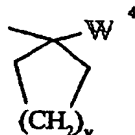
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $S(O)_u$ wherein u is an integer of 0 to 2;

W^1 is a hydroxyl group, a C_{1-10} alkyloxy group, a C_{3-10} cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

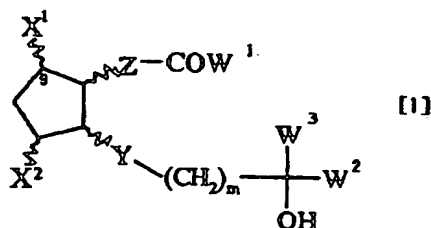
W^2 is a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group, a C_{3-10} cycloalkyl group, a C_{1-5} alkyl group substituted by C_{3-10} cycloalkyl group(s), or a group represented by the formula



wherein W^4 is a C_{1-10} alkyl group, a C_{2-10} alkenyl group, a C_{2-10} alkynyl group or a C_{1-5} alkyl group substituted by C_{3-10} cycloalkyl group(s); v is an integer of 0 to 4;

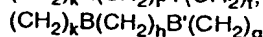
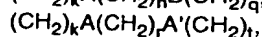
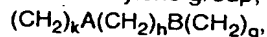
W^3 is a hydrogen atom or a methyl group, or W^3 when taken together with W^2 and the adjacent carbon atom forms a C_{3-10} cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

18. A method of preventing or treating atopic symptoms which comprises administering to a mammal a prophylactically or therapeutically effective amount of a prostaglandin derivative represented by formula [1]

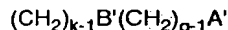


wherein X^1 and X^2 which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula



or



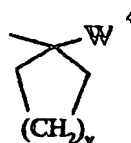
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $\text{S}(\text{O})_u$ wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

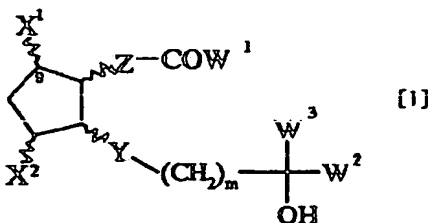
W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

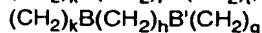
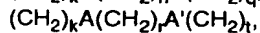
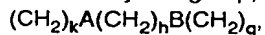
W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, a pharmaceutically acceptable salt thereof or a hydrate thereof.

19. Use of a prostaglandin derivative represented by formula [1] in the manufacture of pharmaceutical preparations for preventing or treating pruritic symptoms:

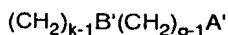


wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula



or



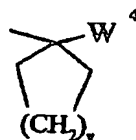
wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $S(O)_u$ wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy group;

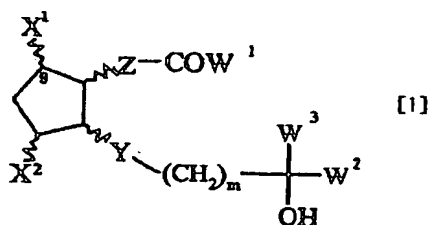
W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1, provided that 7-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-(5Z)-5-heptenic acid is excluded, a pharmaceutically acceptable salt thereof or a hydrate thereof.

20. Use of a prostaglandin derivative represented by formula [1] in the manufacture of pharmaceutical preparations for preventing or treating atopic symptoms:



wherein X¹ and X² which are different from each other represent a hydrogen atom, a halogen atom or a hydroxyl group;

Y is an ethylene group, a vinylene group or an ethynylene group; Z is the formula

$(CH_2)_k A(CH_2)_h B(CH_2)_q$,

$(CH_2)_k A(CH_2)_r A'(CH_2)_t$,

$(CH_2)_k B(CH_2)_h B'(CH_2)_q$

or

$(CH_2)_{k-1} B'(CH_2)_{q-1} A'$

wherein k is an integer of 1 to 4, h is an integer of 0 to 4, q is an integer 1 to 4, r is an integer of 0 to 4, and t is an integer of 0 to 2;

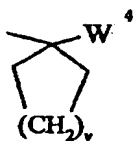
A and A' which may be the same or different represent an ethylene group, a vinylene group or an ethynylene group;

B and B' which may be the same or different represent an oxygen atom or a group represented by the formula $S(O)_u$ wherein u is an integer of 0 to 2;

W¹ is a hydroxyl group, a C₁₋₁₀ alkyloxy group, a C₃₋₁₀ cycloalkyloxy group, an aryloxy group or an arylalkyloxy

group;

W² is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group, a C₃₋₁₀ cycloalkyl group, a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s), or a group represented by the formula



wherein W⁴ is a C₁₋₁₀ alkyl group, a C₂₋₁₀ alkenyl group, a C₂₋₁₀ alkynyl group or a C₁₋₅ alkyl group substituted by C₃₋₁₀ cycloalkyl group(s); v is an integer of 0 to 4;

W³ is a hydrogen atom or a methyl group, or W³ when taken together with W² and the adjacent carbon atom forms a C₃₋₁₀ cycloalkyl group; m is 0 or 1], provided that 7-[(1R,2R,3R,5R)-5-chloro-2-[(1E,3S)-3-cyclohexyl-3-hydroxy-1-propenyl]-3-hydroxycyclopentyl]-(5Z)-5-heptenic acid is excluded, a pharmaceutically acceptable salt thereof or a hydrate thereof.

FIG. 1

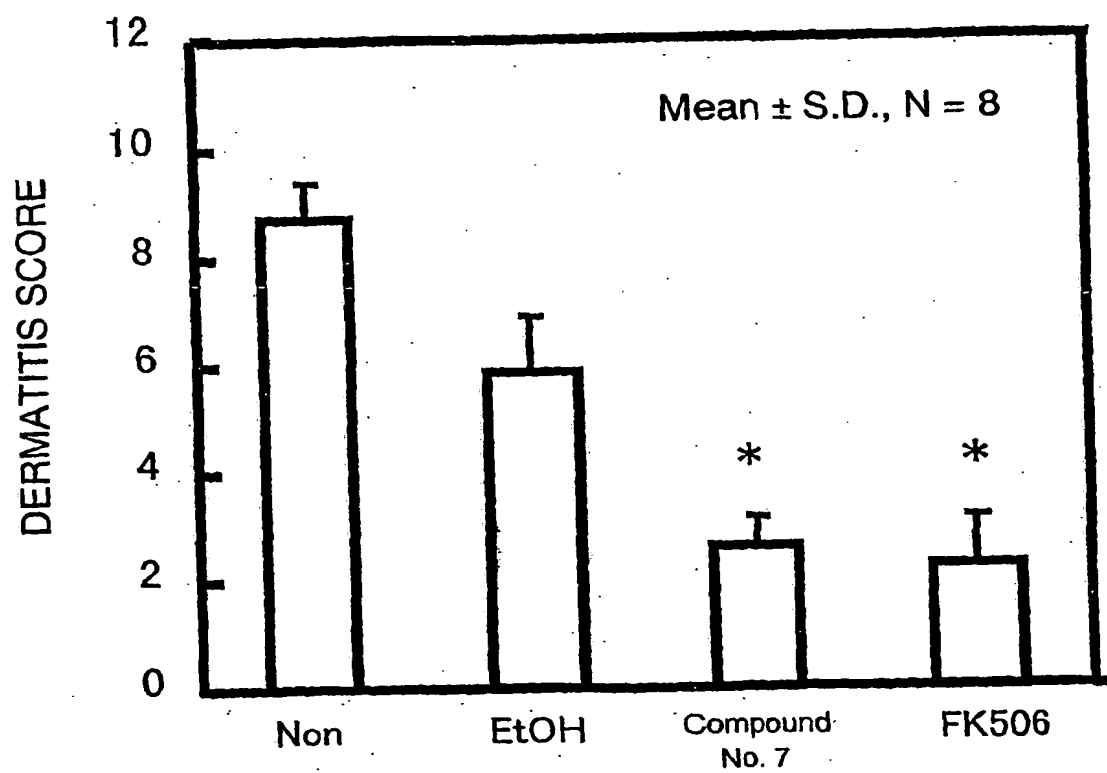


FIG. 2

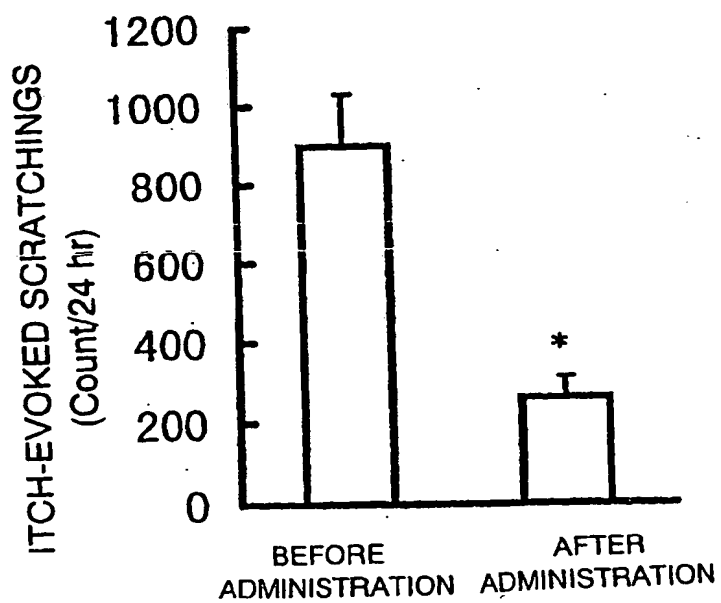
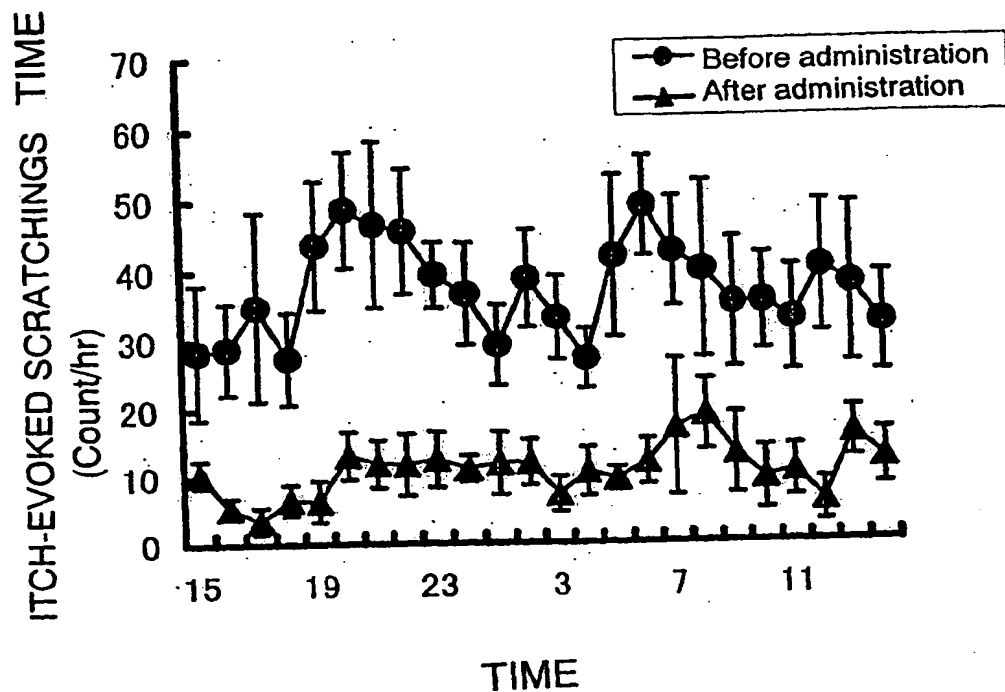


FIG. 3

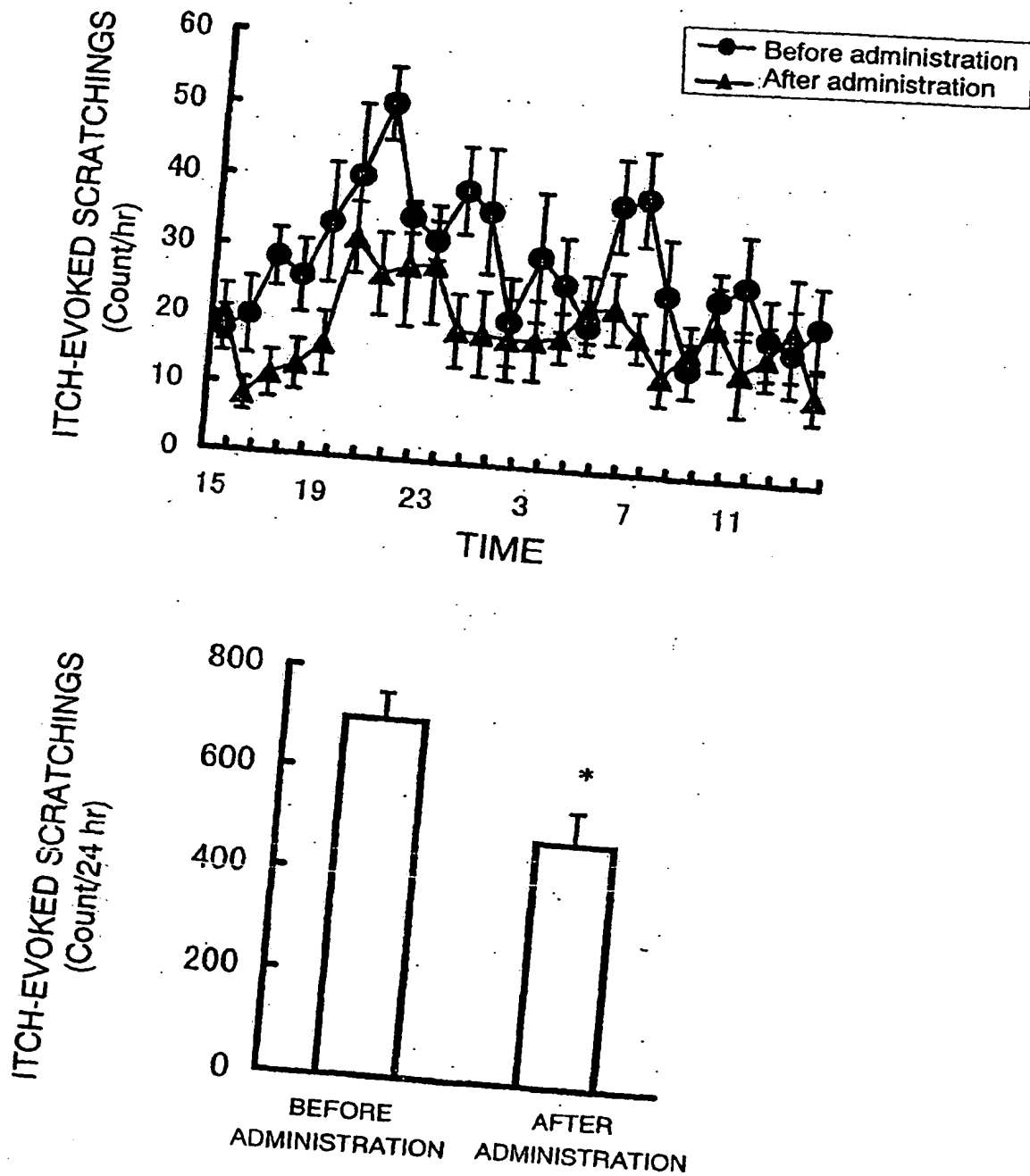
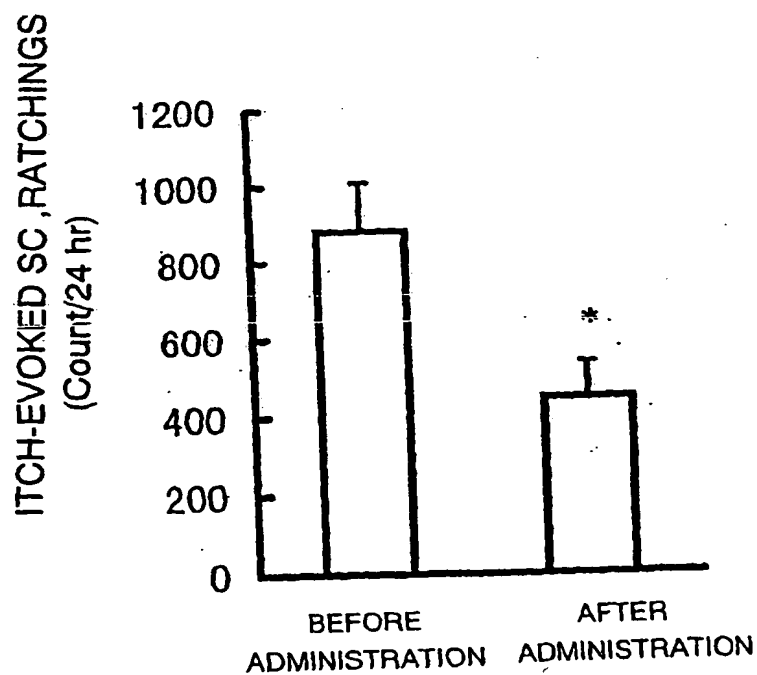
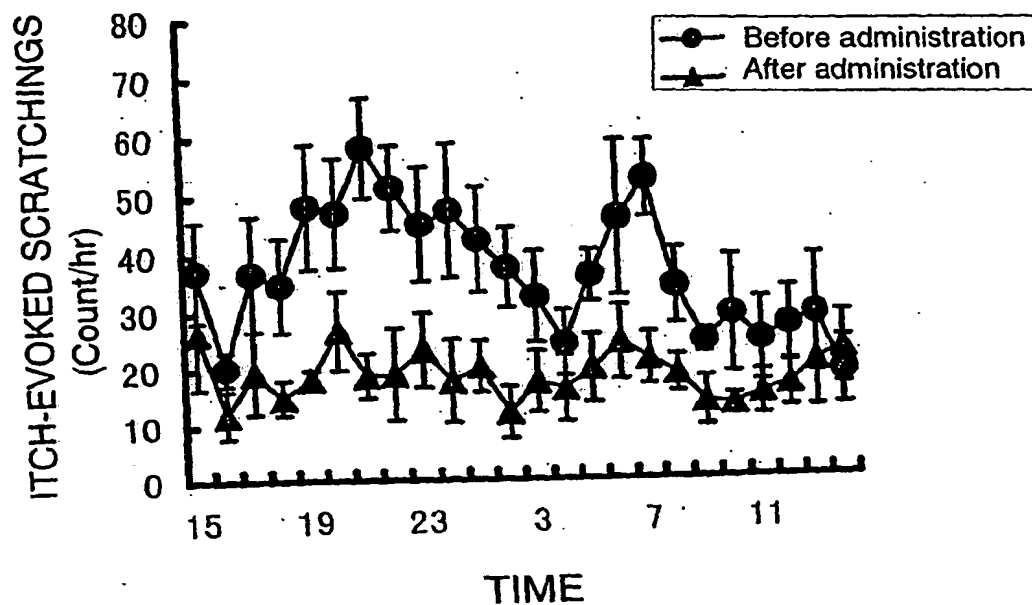


FIG. 4



INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁷ A61K31/5575, A61P17/00, 17/04, 27/02//C07C405/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁷ A61K31/5575, A61P17/00, 17/04, 27/02, C07C405/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), MEDLINE (STN), EMBASE (STN), BIOSIS (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/27971 A1 (KAMM, Michael Albert), 02 July, 1998 (02.07.98), Particularly, Claims; abstract & EP 946155 A1 & US 6635678 B1 & JP 2001-507020 A & AU 9853315 A1 & AU 728889 B2	1, 3-12, 14, 16, 19
Y	EP 1097922 A1 (ONO PHARMACEUTICAL CO., LTD.), 09 May, 2001 (09.05.01), Particularly, Claims; abstract & WO 00/03980 A1 & US 6462081 B1 & JP 2001-089444 A & JP 3174563 B & CA 2336952 A & AU 9946518 A1 & AU 763668 B2 & BR 9912813 A & NZ 509293 A & ZA 2001000295 A & NO 2001000213 A	1-16, 19, 20

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
11 November, 2003 (11.11.03)Date of mailing of the international search report
02 December, 2003 (02.12.03)Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)

Rest Available Copy

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01/49661 A1 (ONO PHARMACEUTICAL CO., LTD.), 12 July, 2001 (12.07.01), Particularly, abstract; Claims & EP 1245562 A1 & US 2003/097023 A1 & US 6639111 B2 & AU 2001022274 A5	1-16, 19, 20
Y	EP 860430 A2 (ONO PHARMACEUTICAL CO., LTD.), 26 August, 1998 (26.08.98), Particularly, Claims; abstract & EP 860430 A3 & EP 860430 B1 & US 6110969 A & US 6576785 B1 & US 2003/186939 A1 & JP 11-193268 A & JP 3162668 B & JP 2000-128858 A & NO 9800442 A & ZA 9800879 A & AT 219054 E & ES 2178808 T3 & CA 2228828 A & AU 9852892 A1 & AU 736271 B2	1-16, 19, 20
Y	WO 99/25358 A1 (ALLERGAN SALES, INC.), 27 May, 1999 (27.05.99), Particularly, Claims; abstract; page 23, lines 9 to 33 & EP 1032395 A1 & US 6124344 A & JP 2001-522893 A & CA 2310630 A & AU 9914616 A1 & BR 9814679 A & NZ 504191 A & NO 2000002217 A	1-16, 19, 20
Y	WO 02/20462 A1 (ONO PHARMACEUTICAL CO., LTD.), 14 March, 2002 (14.03.02), Particularly, abstract; Claims & EP 1314719 A1 & AU 2001078772 A5	1-16, 19, 20
Y	WO 02/16311 A1 (ONO PHARMACEUTICAL CO., LTD.), 28 February, 2002 (28.02.02), Particularly, abstract; Claims & EP 1312601 A1 & AU 2001078771 A5	1-16, 19, 20
Y	WO 89/00559 A1 (SCHERING AG. BERLIN UND BERGKAMEN), 26 January, 1989 (26.01.89), Particularly, abstract; Patentansprüche; page 15, line 23 to page 16, line 5 & EP 299914 A1 & EP 299914 B1 & EP 299914 B2 & US 6225347 B1 & US 5891910 A & JP 2-502009 A & DE 3724189 A1 & DE 3724190 A1 & AU 8820785 A1 & AU 624078 B2 & ZA 8805154 A & HU 51222 A2 & HU 206084 B & IL 87116 A1 & AT 87911 E & CA 1322197 A1 & ES 2054860 T3 & DK 8901327 A & DK 170889 B1	1-16, 19, 20

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

Best Available Copy

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 666256 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 09 August, 1995 (09.08.95), Particularly, Claims; abstract & WO 94/08959 A1 & US 5545666 A & JP 6-192218 A & CA 2147476 A & AU 9351568 A1 & AU 669226 B2	1-16, 19, 20
Y	JP 7-242622 A (TAISHO PHARMACEUTICAL CO., LTD.), 19 September, 1995 (19.09.95), Particularly, abstract; Claims (Family: none)	1-16, 19, 20
Y	EP 737676 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 16 October, 1996 (16.10.96), Particularly, Claims; abstract & WO 95/18101 A1 & JP 7-233144 A & CA 2179981 A & AU 9512827 A1	1-16, 19, 20
Y	JP 7-285929 A (TAISHO PHARMACEUTICAL CO., LTD.), 31 October, 1995 (31.10.95), Particularly, abstract; Claims (Family: none)	1-16, 19, 20
Y	WO 96/16935 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 06 June, 1996 (06.06.96), Particularly, abstract; Claims & JP 8-208599 A & AU 9539364 A1	1-16, 19, 20
Y	JP 9-286775 A (TAISHO PHARMACEUTICAL CO., LTD.), 04 November, 1997 (04.11.97), Particularly, abstract; Claims (Family: none)	1-16, 19, 20
Y	EP 69696 A2 (SCHERING AG. Berlin und Bergkamen), 12 January, 1983 (12.01.83), Particularly, Zusammenfassung, Patentansprüche; page 15, lines 10 to 17 & EP 69696 A3 & EP 69696 B1 & US 4454339 A & US 4789685 A & JP 58-8059 A & JP 4-43906 B & DE 3126924 A1 & CA 1218060 A1 & SU 1301308 A3 & AT 17475 E & CS 236484 B2 & IL 66165 A1 & DK 8202943 A & DK 154073 B & DK 154073 C & AU 8285528 A1 & AU 559449 B2 & ES 513645 A1 & HU 27410 O & HU 190692 B & DK 8701235 A	1-16, 19, 20

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

Best Available Copy

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 85/00367 A1 (SCHERING AG.), 31 January, 1985 (31.01.85), Particularly, abstract; Patentansprüche; page 17, lines 16 to 23 & EP 147461 A1 & EP 147461 B1 & US 4870104 A & US 4983629 A & JP 60-501813 A & JP 6-92362 B & DE 3325175 A1 & AT 71365 E	1-16, 19, 20
Y	WO 85/02841 A1 (SCHERING AG.), 04 July, 1985 (04.07.85), Particularly, abstract; Patentansprüche; page 16, lines 1 to 8 & EP 198829 A1 & EP 198829 B1 & US 4699920 A & JP 61-500787 A & JP 6-8280 B & DE 3347128 A1 & AT 52078 E	1-16, 19, 20
Y	EP 652211 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 10 May, 1995 (10.05.95), Particularly, Claims; abstract & WO 94/02457 A1 & US 5491254 A & AU 664915 B2 & AU 9345137 A1	1-16, 19, 20
Y	EP 1082961 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 14 March, 2001 (14.03.01), Particularly, Claims; abstract & WO 99/61029 A1 & US 6395786 B1 & JP 2000-44477 A & CA 2333038 A & AU 9938514 A1 & AU 742232 B2	1-16, 19, 20
Y	EP 1083168 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 14 March, 2001 (14.03.01), Particularly, Claims; abstract & EP 1083168 B1 & US 6329539 B1 & WO 99/61419 A1 & JP 2000-44477 A & CA 2334355 A & AU 9938512 A1 & AU 742118 B2	1-16, 19, 20
Y	EP 1211242 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 05 June, 2002 (05.06.02), Particularly, Claims; abstract & WO 01/19790 A1	1-16, 19, 20
Y	US 5807892 A (Alcon Laboratories, Inc.), 15 September, 1998 (15.09.98), Particularly, Claims; abstract (Family: none)	1-16, 19, 20
Y	JP 2000-273083 A (TAISHO PHARMACEUTICAL CO., LTD.), 03 October, 2000 (03.10.00), Particularly, abstract; Claims; Par. No. [0033] (Family: none)	1-16, 19, 20

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

Rest Available Copy

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 2001-122786 A (TAISHO PHARMACEUTICAL CO., LTD.), 08 May, 2001 (08.05.01), Particularly, abstract; Claims; Par. No. [0036] (Family: none)	1-16, 19, 20
Y	JP 2001-089443 A (TAISHO PHARMACEUTICAL CO., LTD.), 03 April, 2001 (03.04.01), Particularly, abstract; Claims; effect of the invention (Family: none)	1-16, 19, 20
Y	JP 2001-151749 A (TAISHO PHARMACEUTICAL CO., LTD.), 05 June, 2001 (05.06.01), Particularly, abstract; Claims; Par. No. [0034] (Family: none)	1-16, 19, 20
P, X	WO 03/070252 A1 (TAISHO PHARMACEUTICAL CO., LTD.), 28 August, 2003 (28.08.03), Full text (Family: none)	1-16, 19, 20

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

Best Available Copy

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP03/10051

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

- 1.
- ☒
- Claims Nos.: 17, 18

because they relate to subject matter not required to be searched by this Authority, namely:

Claims 17, 18 pertain to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

- 2.
- ☐
- Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

- 3.
- ☐
- Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

Best Available Copy